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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/716,580	11/18/2003	Ralph Mocikat	080306-000100US	6256

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EXAMINER	
WOODWARD, CHERIE MICHELLE	
ART UNIT	**PAPER NUMBER**
1647	

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01/06/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/716,580	MOCIKAT, RALPH	
	Examiner	Art Unit	
	CHERIE M. WOODWARD	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-9,11-17 and 29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-9,11-17 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

1. Applicants Response and Amendments filed 10/3/2008 are acknowledged and entered. Claims 1-5, 7-9, 11-17 and 29 are pending and under examination. It is noted that Applicant incorrectly listed the status identifier for claim 29 as withdrawn.

Response to Arguments

Claim Rejections Maintained

Claim Rejections - 35 USC § 112, First Paragraph

Written Description

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-5, 7-9 and 11-17 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for the reasons of record and the reasons set forth herein.

Applicant argues that the common components of the vector are provided and that the skilled artisan would have sufficient common knowledge of the common components of the claimed vector and how to acquire them (Remarks, p. 6, last paragraph). In response to the examiner's citation of University of Rochester v. GD Searle & Co, 69 USQP2d 1886 (Fed. Cir. 2004) and Ex parte Kubin, 83 USPQ2d 1410 (BPAI, 2007), Applicant argues that the fact pattern in the instant application is distinguished from that of Rochester or Kubin (Remarks, p. 6, last paragraph to p. 7, first paragraph). Applicant also argues that the examiner's analysis of a representative number of species or common structural features have no relevance in the present case (Remarks, p. 6, last paragraph). Applicant argues that the DNA sequences encoding a whole or partial antibody constant region are known in the art and described in the specification (Remarks, p. 7, first paragraph). Applicant argues that the large number of possible selections within each genus of known components is evidence of a broad scope of enablement and possession of the invention (Remarks, p. 7, first paragraph). Applicant argues that this broad scope is not "akin to the hunting for the unknown referred to by the Supreme Court in *Brenner*" (Remarks, p. 7, first paragraph). Applicant argues that one's ability to choose from a broad range of known components to

practice a claimed invention supports the conclusion of Applicant's possession of the invention (Remarks, p. 7, first paragraph). Applicant's arguments have been fully considered, but they are not persuasive.

Applicant's arguments are based on the proposition that the genera of claimed vectors can be made by one of skill in the art by obtaining the required components. The components of the claimed vector comprise nucleic acid sequences of "at least 1.5kb." Simply knowing the nucleic acid code of a μ intron or κ intron is not sufficient to describe a representative number of species or to adequately show possession when the claim limitations, as written, recite "at least" 1.5kb.

Contrary to Applicant's argument, Applicant has not shown or provided any evidence that Applicant was in possession of a sufficient representative number of species of the claimed genera at the time the application was filed. Further, contrary to Applicant's arguments, the examiner's analysis of a representative number of species or common structural features is very relevant to the present case and to the broad genera of subject matter encompassed by the claims, as written. 35 USC 112, first paragraph, the regulations concerning written description (as set forth under 37 CFR), and the written description case law make the relevance of a genus/species analysis very relevant to broad genus claims (see the case law cited of record and set forth herein). In the instant claims and the specification, Applicant has shown nothing more than by making, experimenting, and testing the "characteristic components" of the invention, one of skill in the art may thereby obtain possession. The ability to "obtain" possession is distinguished from the requirement that applicant be in possession of the claimed subject matter at the time the application is filed.

When considering whether Applicant has disclosed a sufficient representative number of species, the "representative number of species" means that the species which are adequately described are representative of the entire genus. When there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See Enzo Biochem, 323 F.3d at 966, 63 USPQ2d at 1615. Further, in The Regents of the University of California v. Eli Lilly and Co, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed Cir. 1997) the Court held that the written description requirement not satisfied by merely providing "a result that one might achieve if one made that invention"(see also In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming a rejection for lack of written description because the specification does "little more than outline goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate")).

As previously stated in the Office Actions of 18 October 2007 and 3 April 2008, it is well understood that possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features (see, Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 927, 69 USPQ2d 1886, 1895 (Fed. Cir. 2004); accord Ex Parte Kubin, 2007-0819, BPAI 31 May 2007, opinion at p. 16, paragraph 1). Applicant's argument that the Rochester and Kubin cases differ on their fact pattern from the instant case does not diminish the case holdings that possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features. The instant claims and specification do nothing more than suggest various components in the form of generic lists or as a "laundry list" of potential components that one of ordinary skill in the art could piece together to obtain possession of the claimed genus of vectors. In this sense, the instant case is on point with Rochester and Kubin because all that has been disclosed is a description of how to obtain possession. See also, Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species).

In the instant application only one species of the claimed invention is disclosed in the specification (see pages 13-14 of the specification, labeled pages 17 and 18) as a vector comprising pSP72(ΔEV)-mGM-CSF (ΔL) cloned into pSVgpt-huγ1-A5. When one contrasts this species of vector against the claimed genera of vectors and vector components comprising the claimed vectors, the difference in the scope of the singular representative species of vector and the scope of the broader claimed genera becomes clear. Neither the specification nor the art provide a sufficient description to show that Applicant was in possession of vectors comprising a sufficient number of the following components linked together, as claimed: a genera of vectors encoding a generic genus cytokine-immunoglobulin fusion proteins; a genera of vectors encoding a generic genus of immunoglobulins; a genera of vectors comprising DNA encoding a generic genus of cytokines; a genera of vectors encoding a generic genus of marker genes; a genera of vectors encoding a generic genus of enhancers; a genera of vectors encoding a genus of nucleic acids homologous to a region comprising the Cμ or Cκ enhancer; a genera of vectors encoding a generic genus bacterially compatible regulatory units; a genera of vectors encoding generic genus of domains from a human immunoglobulin chain; a genera of vectors encoding a generic genus of interleukins; a genera of vectors encoding a generic genus of interferons; a genera of vectors encoding a generic genus of colony-stimulating factors; a genera of vectors encoding a generic genus of lymphokines; and a genera of vectors encoding a generic genus of growth factors.

The examiner notes specific embodiments of the cytokines IL-2, IL-4, IL-7, IL-12, IL-13, GM-CSF and IFNγ are set forth in claim 16 (which is dependent only on claims 1 and 15), but this claim does not provide a limitation for the genus of enhancers, marker genes, bacterially compatible regulatory units, domains from a human immunoglobulin chain, or even the species from which these cytokines are to be obtained (i.e. human, rat, mouse, cat, dog, goat, cow, chicken, sheep, etc), such that one of ordinary skill in the art would understand that Applicant was in possession of the genera of claimed vectors encoding all generic cytokines from a representative number of species at the time the application was filed. Similarly, claim 17, which is dependent only on claim 1, recites specific marker genes, but does not provide any limitations of the genus of enhancers, bacterially compatible regulatory units, domains from a human.

Other than Applicant's example of a vector comprising pSP72(ΔEV)-mGM-CSF (ΔL) cloned into pSVgpt-huγ1-A5, and the vectors taught in the art (*supra*) the skilled artisan is left to figure out which of the components from the large claimed genera of "at least 1.5kb" to pick and choose to construct a vector. The specification does not disclose any particular DNA sequences from the genus of cytokines such that one of ordinary skill in the art would understand which species the DNA was to be obtained from or whether DNA encoding specific domains of the cytokines were to be included or excluded (i.e. only domains from the soluble region of the proteins encoded by the DNA) (see In re Smith, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972) (holding that a subgenus is not necessarily implicitly described by a genus encompassing it and a species upon which it reads)).

Additionally, the immunoglobulin kappa locus is not comprised of one single gene and cannot be thought of in the same sense one would think of a simple gene model comprising 5' to 3' introns and exons with an enhancer and promoter located 5' of the coding sequence. Rather, the Ig kappa locus is comprised of numerous kappa variable regions (see, for evidentiary purposes only in response to Applicant's argument, the NCBI Genecard for IGK@, last accessed 1/3/2009). The immunoglobulin kappa locus is a very broad gene region spanning 383864 base pairs (see also NCBI NG_000833. Homo sapiens immunoglobulin kappa locus, last accessed 1/3/2009, cited in response to Applicant's arguments). Applicant's attention is directed to the summary on page 2 of 118 of the NCBI report (attached). The summary states that "[t]he kappa locus comprises two clusters of genes. The proximal cluster includes multiple V (variable) and J (joining) segments and a single C (constant) segment, while the distal cluster includes duplicated versions of 36 V segments found in the proximal cluster." Interspersed among these coding exon regions are numerous introns of widely varying base pair length and polynucleotide composition. The mu locus is similarly situated.

Even though the sequence of the immunoglobulin kappa locus (for example) is known, the skilled artisan would not be readily apprised that Applicant was in possession of a vector comprising an at least 1.5kb segment from one or more of the kappa introns. The limited disclosures in the specification do not remedy this problem because the specification simply does not disclose a sufficient number of representative species of the various kappa intron components (from the numerous potential introns of the kappa gene locus comprising more than 383,000 base pairs), such that the Applicant can show possession of the invention as claimed.

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genera of vectors to establish that Applicant was in possession of the vectors in their full scope. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus, as claimed, at the time the application was filed.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 1-5, 7-9, 11, 13-17, and 29 remain rejected under 35 U.S.C. 102(e) as being anticipated by Polack et al., US Patent 6,521,449 (18 February 2003, benefit to 12 September 1996) as evidenced by Mucke et al., (Gene Therapy. 1997 Feb;4:82-92) (both previously cited of record), for the reasons of record and the reasons set forth herein.

Applicant argues that Applicant Polack et al., as evidenced by Mucke et al., do not provide all of the limitations of the pending claims (Remarks, p. 7, last paragraph). Applicant argues that the phraseology "a region of at least 1.5kb which is homologous to an at least 1.5kb segment of a μ intron or κ intron" cannot be found in the references (Remarks, p. 7, last paragraph). Applicant argues that the instant claims should be read as the 1.5kb region being continuous, unlike the teachings in Polack (as evidenced by Figure 1(b) of Mucke et al) which disclose the use of two enhancer κ intron elements, Ei and E3' which total to more than 1.5kb (Remarks, p. 7, last paragraph to p. 8, first paragraph). Applicant

argues that the specification explains that region homologous to an at least a 1.5 kb region is required to ensure successful recombination (Remarks, p. 8, first paragraph). Applicant argues that the continuity of the at least 1.5kb region is "inherently continuous…because otherwise there would be no recombination or site-specific recombination" (Remarks, p. 8, first paragraph). Applicant also argues that the length of the enhancers in the BC219 vector taught by the '449 patent and evidenced by Mucke et al., is not at least 1.5kb in length (Remarks, p. 8, first paragraph). Applicant argues that the E3' enhancer shown in Figure 1(b) of Mucke et al., is not part of the κ intron, but that it is located 3' to the human Ig kappa light chain gene locus (Remarks, p. 8, last paragraph). Applicant argues that introns by definition are untranslated sequences within a gene and not sequences located at a position 3' to the gene (Remarks, p. 8, last paragraph). Applicant's arguments have been fully considered, but they are not persuasive.

Regarding Applicant's argument directed to the specific phraseology, the art does not have to recite the claimed range, *ipsa verba*, as long as the art teaches a composition within the claimed range that meets the limitation of the claims, as written. The '449 patent teaches "[a] gene construct containing, in functional association, at least: (a) (i) a combination of two enhancer elements of the immunoglobulin kappa locus, namely the kappa intron enhancer (kappa Ei) and the kappa 3' enhancer (kappa E3'); or (ii) a combination of two enhancer elements of the immunoglobulin heavy chain mu locus, namely mu Ei and the mu E3' enhancer region located 3' of C alpha; or (iii) a combination of one or more of these enhancer elements of (ii) together with one or more of the aforementioned elements of the immunoglobulin kappa locus" (column 4, line 39-42). The combination of kappa E3' and kappa Ei enhancers, as taught by the '449, exceed the claim limitation of being "at least 1.5kb" in length. Applicant's argument as to the length of the enhancers taught by the '449 patent is without merit, as the reference speaks for itself. Moreover, the Mucke et al., reference was cited as an evidentiary reference to show the inherent features of the '449 patent, both references demonstrate that the length of the kappa E3' segment is 881bp long and the kappa Ei segment is 1486bp long, as exemplified in the BC219 vector.

Regarding Applicant's argument directed to the "continuity" of the at least 1.5kb region, the claims do not require that the region be continuous. Instead the claims merely recite that the selected region be homologous to an at least 1.5kb segment of a μ intron or κ intron. Applicant's argument that unless the region is continuously at least 1.5kb in length or it will not work is not supported by any evidence. Applicant is specifically directed to the teachings of Polack et al., as evidenced by Mucke et al., who teach that such a segment does in fact work. If Applicant wishes to distinguish the instant invention over the prior art, Applicant should consider amending the claim language to state that the segment be an at least 1.5kb or greater continuous segment from a μ intron or κ intron.

Regarding Applicant's argument that the E3' enhancer shown in Figure 1(b) of Mucke et al., is not part of the κ intron, but that it is located 3' to the human Ig kappa light chain gene locus and that introns by definition are untranslated sequences within a gene and not sequences located at a position 3' to the gene. Applicant is directed to Pongubala et al., (Mol Cell Biol. 1991 Feb;11(2):1040-1047) (cited only as an evidentiary reference in response to Applicant's argument), which specifically teaches the function and characterization of the E3' enhancer from the immunoglobulin kappa chain and states that it is located 8.5kb downstream of the kappa constant-region exon. Pongubala et al., teach that S107 plasma cytoma cells lack NF-B and therefore do not exhibit intron enhancer activity, but that the endogenous kappa genes are still transcriptionally active due to this E3' enhancer (p. 1045, column 2, first full paragraph). Additionally, the immunoglobulin kappa locus is not comprised of one single gene and cannot be thought of in the same sense one would think of a simple gene model comprising 5' to 3' introns and exons with an enhancer and promoter located 5' of the coding sequence. Rather, the Ig kappa locus is comprised of numerous kappa variable regions (see, for evidentiary purposes only in response to Applicant's argument, the NCBI Genecard for IGK@, last accessed 1/3/2009). The location of the E3' enhancer 3' to the kappa constant region is not indicative of the E3' enhancer being located "after the stop codon" in a more simplistic model. Simply put, the immunoglobulin kappa locus is a very broad gene region spanning 383864 base pairs (see NCBI NG_000833. Homo sapiens immunoglobulin kappa locus, last accessed 1/3/2009, cited as an exemplary reference only, in response to Applicant's arguments). Applicant's attention is directed to the summary on page 2 of 118 of the NCBI report (attached). The summary states that "[t]he kappa locus comprises two clusters of genes. The proximal cluster includes multiple V (variable) and J (joining) segments and a single C (constant) segment, while the distal cluster includes duplicated versions of 36 V segments found in the proximal cluster." Accordingly, the kappa E3' enhancer, which is located 8.5kb downstream of the kappa constant region exon, is still well within the kappa gene locus and is located 5' of the distal variable region segments (this would be prior to a stop codon in an elementary gene model) and is a non-coding region, which qualifies it as being in an intron. Applicant's attention is also directed to the '449 patent, Figure 1, which shows that the E3' enhancer is considered to be within the Ig kappa locus. As such, the art of record anticipates the invention as claimed.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-5, 7-9, 11-13, and 15-17 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Polack et al., US Patent 6,521,449 (18 February 2003, benefit to 12 September 1996), Levy et al., US Patent 6,099,846 (8 August 2000, benefit to 14 April 1995), and Gillies et al., US Patent 5,650,150 (22 July 1997, benefit to 7 November 1991), as evidenced by Mucke et al., (Gene Therapy. 1997 Feb;4:82-92) (previously cited of record), for the reasons of record and the reasons set forth herein.

Applicant combines the arguments to both rejections under 35 USC 103(a).

Applicant argues that the combination of references does not support a *prima facie* case of obviousness (Remarks, p. 9, third full paragraph). Applicant argues that the person of ordinary skill in the art would have no reason or motivation to replace the enhancers used by the ‘449 patent with the 2.3kb mouse μ intron sequence used by Mocikat et al., to modify the expression vector of the '449 patent (Remarks, p. 10, first paragraph). Applicant argues that the ‘449 patent uses the enhancers to facilitate or

augment the expression of a gene of interest and that replacing the enhancers with the 2.3kb mouse μ intron sequence would defeat this purpose (Remarks, p. 10, first paragraph). Applicant argues that because there is at least one obvious reason not to combine the references, no *prima facie* case of obviousness can be established (Remarks, p. 10, first paragraph). Applicant's arguments have been fully considered and they are not persuasive.

The Mocikat et al., reference provides the motivation and rationale to combine the references. Mocikat et al., teach a vector comprising a 2.3kb HindIII fragment from the mouse μ intron sequence (p. 159, column 2, last paragraph to p. 160, column 1, first paragraph). HindIII is an old and well-known type II restriction endonuclease that is routinely used in DNA sequencing, gene analysis and cloning. Mocikat et al., discloses that gene replacement results in higher expression rates than vector integration because it has been found that replacement events tend to separate the selection marker from the vector sequence and that a close proximity of the selection marker to the immunoglobulin expression unit may exert an adverse effect on immunoglobulin transcription (p. 161, column 2, last paragraph and p. 162, column 2, first paragraph). Mocikat et al., demonstrated that hybridoma cell lines generated as replacement constructs using the 2.3kb HindIII fragment from the mouse μ intron did not present the same adverse issues when the selection marker was placed in relative proximity to the immunoglobulin expression unit (p. 161, column 2, first and second full paragraphs; Figures 1 and 3b, lanes 2 and 4). Mocikat et al., also explains that replacement constructs using gene targeting may be preferable to gene integration in hybridomas because of the ease and rapidity of manipulation circumventing the need to isolate V genes to perform selection schemes over periods of months and to use toxic drugs (p. 162, column 2, last paragraph). Mocikat et al., provide the rationale and motivation for combining and/or substituting the 2.3kb mouse μ intron sequence comprising a HindIII fragment to create expression vectors capable of producing an immunoglobulin-cytokine gene replacement construct hybridoma would result in constructs that would be easier to use due to the rapidity of manipulation, time savings, and not having to engage in toxic drug selection. Accordingly, the teachings of Mocikat et al., show that Applicant's argument that the combined use and/or substitution of the enhancers of the '449 patent to facilitate or augment the expression of a gene of interest would defeat the purpose of the enhancer, are without evidentiary support. Contrary to Applicant's arguments, Mocikat et al., show that the use of the 2.3kb HindIII fragment from the mouse μ intron would in fact be beneficial by making the production of replacement construct hybridomas easier and more commercially viable as selection and testing time cycles would be greatly reduced.

10. Claims 1-5, 7-9 and 11-17 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Mucke et al., (Gene Therapy. 1997 Feb;4:82-92), Polack et al., US Patent 6,521,449 (18 February 2003, benefit to 12 September 1996) and Mocikat et al., (Immunology. 1995:84:159-163) for the reasons of record and the reasons set forth herein.

Applicant combines the arguments to both rejections under 35 USC 103(a).

As set forth above, Applicant argues that the combination of references does not support a *prima facie* case of obviousness (Remarks, p. 9, third full paragraph). Applicant argues that the person of ordinary skill in the art would have no reason or motivation to replace the enhancers used by the '449 patent with the 2.3kb mouse μ intron sequence used by Mocikat et al., to modify the expression vector of the '449 patent (Remarks, p. 10, first paragraph). Applicant argues that the '449 patent uses the enhancers to facilitate or augment the expression of a gene of interest and that replacing the enhancers with the 2.3kb mouse μ intron sequence would defeat this purpose (Remarks, p. 10, first paragraph). Applicant argues that because there is at least one obvious reason not to combine the references, no *prima facie* case of obviousness can be established (Remarks, p. 10, first paragraph). Applicant's arguments have been fully considered and they are not persuasive.

The Mocikat et al., reference provides the motivation and rationale to combine the references. Mocikat et al., teach a vector comprising a 2.3kb HindIII fragment from the mouse μ intron sequence (p. 159, column 2, last paragraph to p. 160, column 1, first paragraph). HindIII is an old and well-known type II restriction endonuclease that is routinely used in DNA sequencing, gene analysis and cloning. Mocikat et al., discloses that gene replacement results in higher expression rates than vector integration because it has been found that replacement events tend to separate the selection marker from the vector sequence and that a close proximity of the selection marker to the immunoglobulin expression unit may exert an adverse effect on immunoglobulin transcription (p. 161, column 2, last paragraph and p. 162, column 2, first paragraph). Mocikat et al., demonstrated that hybridoma cell lines generated as replacement constructs using the 2.3kb HindIII fragment from the mouse μ intron did not present the same adverse issues when the selection marker was placed in relative proximity to the immunoglobulin expression unit (p. 161, column 2, first and second full paragraphs; Figures 1 and 3b, lanes 2 and 4). Mocikat et al., also explains that replacement constructs using gene targeting may be preferable to gene integration in hybridomas because of the ease and rapidity of manipulation circumventing the need to isolate V genes to perform selection schemes over periods of months and to use toxic drugs (p. 162, column 2, last paragraph). Mocikat et al., provide the rationale and motivation for combining and/or substituting the 2.3kb mouse μ intron sequence comprising a HindIII fragment to create expression vectors capable of

producing an immunoglobulin-cytokine gene replacement construct hybridoma would result in constructs that would be easier to use due to the rapidity of manipulation, time savings, and not having to engage in toxic drug selection. Accordingly, the teachings of Mocikat et al., show that Applicant's argument that the combined use and/or substitution of the enhancers of the '449 patent to facilitate or augment the expression of a gene of interest would defeat the purpose of the enhancer, are without evidentiary support. Contrary to Applicant's arguments, Mocikat et al., show that the use of the 2.3kb HindIII fragment from the mouse μ intron would in fact be beneficial by making the production of replacement construct hybridomas easier and more commercially viable as selection and testing time cycles would be greatly reduced.

Conclusion

NO CLAIM IS ALLOWED.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHERIE M. WOODWARD whose telephone number is (571)272-3329. The examiner can normally be reached on Monday - Friday 9:30am-6:00pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cherie M. Woodward/
Primary Examiner, Art Unit 1647